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Childhood adversity increases vulnerability for behavioral symptoms and immune dysregulation in women with breast cancer

Linda Witek Janusek [a,*], Dina Tell [a], Kevin Albuquerque [b], Herbert L. Mathews [b]

[a] Marcella Niehoff School of Nursing, Loyola University Chicago, Health Science Division, Maywood, IL 60153, United States
[b] Stritch School of Medicine, Loyola University Chicago, Health Science Division, Maywood, IL 60153, United States

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ABSTRACT

Women respond differentially to the stress-associated with breast cancer diagnosis and treatment, with some women experiencing more intense and/or sustained behavioral symptoms and immune dysregulation than others. Childhood adversity has been identified to produce long-term dysregulation of stress response systems, increasing reactivity to stressors encountered during adulthood. This study determined whether childhood adversity increased vulnerability for more intense and sustained behavioral symptoms (fatigue, perceived stress, and depressive symptoms), poorer quality of life, and greater immune dysregulation in women ($N = 40$) with breast cancer. Evaluation was after breast surgery and through early survivorship. Hierarchical linear modeling was used to examine intra-individual and inter-individual differences with respect to initial status and to the pattern of change (i.e. trajectory) of outcomes. At initial assessment, women exposed to childhood emotional neglect/abuse had greater perceived stress, fatigue, depressive symptoms and poorer quality of life, as well as lower natural killer cell activity (NKCA). Although these outcomes improved over time, women with greater childhood emotional neglect/abuse exhibited worse outcomes through early survivorship. No effect was observed on the pattern of change for these outcomes. In contrast, childhood physical neglect predicted sustained trajectories of greater perceived stress, worse quality of life, and elevated plasma IL-6; with no effect observed at initial assessment. Thus, childhood adversity leaves an enduring imprint, increasing vulnerability for behavioral symptoms, poor quality of life, and elevations in IL-6 in women with breast cancer. Further, childhood adversity predisposes to lower NKCA at a critical time when this immune-effector mechanism is most effective at halting nascent tumor seeding.

1. Introduction

Any cancer diagnosis evokes fear and dread, but for women a diagnosis of breast cancer is especially devastating, as breast cancer is the second leading cause of cancer death in American women (American Cancer Society, 2011). Women diagnosed with breast cancer experience increased stress perception, anxiety, and mood disturbance (Bower, 2008; Witek-Janusek et al., 2008; Witek-Janusek et al., 2007) and the emotional response to breast cancer is independent of disease stage, as women with early stage non-invasive breast cancers also react emotionally to a breast cancer diagnosis (Beatty et al., 2008; Rakovitch et al., 2003; Witek-Janusek et al., 2007). Such emotional distress is often accompanied by depressive symptoms and fatigue, which emerge at diagnosis (Witek-Janusek et al., 2007) and intensify with treatment (Maraste et al., 1992; Schreier and Williams, 2004). For most women psychological distress dissipates in the months after treatment; yet for some women depressive symptoms and fatigue continue beyond treatment and persist into survivorship (Bower et al., 2000; Ganz et al., 1998). Recently, individual differences in the trajectories (intensity and duration) of distress, depressive symptoms and fatigue have been described for women from the time of their breast cancer diagnosis through early cancer survivorship. Those studies identify individual heterogeneity in the behavioral response to breast cancer, with a sizable number of women exhibiting greater vulnerability to the emotional challenges associated with cancer than others (Dhruva et al., 2010; Dunn et al., 2011; Henselmans et al., 2010). Such findings emphasize the importance of identifying vulnerability factors that contribute to individual differences in the psychological response to and recovery from a traumatic life event, like breast cancer.

Childhood adversity has been identified as a vulnerability factor, giving rise to an adult phenotype characterized by heightened reactivity to stress (Danese and McEwen, 2011; Heim et al., 2010; Nemeroff, 2004). Multiple studies document that early life stress

* Corresponding author. Address: Marcella Niehoff School of Nursing, Loyola University Chicago, Maguire Center, 2160 S. First Ave., Maywood, IL, United States. Tel.: +1 708 216 9661; fax: +1 708 216 9555.
E-mail address: LJanuse@luc.edu (L. Witek Janusek).

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alters neurobiological processes of the brain during development, a time when the brain is more malleable and thus more susceptible to adverse environmental stimuli (Danese and McEwen, 2011; Heim et al., 2010; Nemeroff, 2004). Adults exposed to childhood adversity manifest greater emotional responsiveness to stress (McLaughlin et al., 2010a), as well as a greater physiological response to stress, including increased autonomic nervous system and dysregulated hypothalamic-pituitary-adrenocortical (HPA) axis reactivity (Heim et al., 2008). Individuals with a history of adversity during childhood are at greater risk for depression and other mood disorders later in life, especially in the context of additional challenge (Chen et al., 2010b; Heim et al., 2010; Hill et al., 2000; Nemeroff, 2004).

Prior work also demonstrates that early life adversity predisposes to a proinflammatory phenotype. For example, lower childhood socioeconomic status, and presumably more adverse early life experiences, was reported to be associated with higher circulating levels of IL-6 (Carroll et al., 2011). Moreover, in a longitudinal study, childhood maltreatment was found to predict risk for low grade inflammation in adults; and this effect was independent of other risk factors, such as adult and child socioeconomic status and health behaviors (Danese et al., 2007). In the context of stressful challenge, previous work demonstrates that childhood adversity predisposes to an exaggerated proinflammatory response. When subjected to an acute laboratory social evaluative stress test (Trier Social Stress Test – TSST), healthy adults with exposure to childhood maltreatment exhibited a greater elevation in plasma IL-6, compared to those without a history of childhood maltreatment (Carpenter et al., 2010). Consistent with this observation, older adults exposed to childhood adversity were found to have greater circulating IL-6 and TNF-alpha levels when experiencing the naturalistic and chronic stress associated with caregiving for others with dementia (Kiecolt-Glaser et al., 2010). Such a proinflammatory phenotype linked to early life adversity may emerge during young adulthood, as peripheral blood mononuclear cells (PBMC) derived from young women raised in a harsh family climate produced more IL-6 in response to *in vitro* challenge with lipopolysaccharide and in response to real life psychological stressors (Miller and Chen, 2010).

Little is known about the effect of early life stress in patient populations, such as individuals diagnosed with cancer. In particular, there is a lack of understanding of the effects of early life stress on immune outcomes relevant to cancer control, such as NKCA and the proinflammatory cytokine, IL-6. IL-6 is notable for its pleiotropic tumor promoting activities including anti-apoptotic, pro-invasive, and immune-stimulatory effects attributable to the activation of Stat3 target genes (D'Anello et al., 2010; Hartman et al., 2011; Kishimoto, 2005; Knupfer and Preiss, 2007). There is an increasing literature in breast cancer patients indicating that high serum IL-6 is an independent negative prognostic indicator (Knupfer and Preiss, 2007). In patients with metastatic breast cancer, circulating IL-6 is associated with worse survival and at later stages of breast cancer progression IL-6 may have a net stimulatory effect on tumor growth (Knupfer and Preiss, 2007). Further, inflammation is thought to contribute to the development and progression of various cancers, including breast (Van der Auwera et al., 2004). IL-6 also up-regulates VEGF expression in several tumors via Stat3 activation of the gp130/Jak pathway and this type of up-regulation has been observed in various cancers (Goldberg and Schwertfeger, 2010; Huang et al., 2004; Steiner et al., 2004) and may be vital to the angiogenic process that occurs in tumors, maintaining and/or driving their growth.

NK cells contribute to cancer defense (Vivier et al., 2011) and previous studies show that on average women experiencing the stress associated with breast cancer diagnosis exhibit reductions in NKCA (Thornton et al., 2007; Witek-Janusek et al., 2008; Witek-Janusek et al., 2007). Also, women who report greater subjective stress after breast cancer surgery, but prior to adjuvant therapy, have lower basal and interferon augmented NKCA (Andersen et al., 1998, 2004). Yet, the extent of immune dysregulation at breast cancer diagnosis and the rate of recovery post-treatment show individual variation, which is associated with subjective stress perception. Thornton et al., demonstrated that women who showed an early decline in stress perception after their breast cancer surgery also showed the most rapid recovery of NKCA (Thornton et al., 2007). Optimal NKCA is relevant to women with breast cancer. NK cells defend against tumor initiation and tumor metastasis and breast cancer is an epithelial tumor that is susceptible to the anti-tumor effects of NK cells (Avraham and Ben-Eliyahu, 2007; Ben-Eliyahu, 2003; Dighe et al., 1994; Kagi et al., 1994; Kaplan et al., 1998; Lutgendorf et al., 2007; Seki et al., 2003; Smyth et al., 1998; Smyth et al., 1999; Stojanovic and Cerwenka, 2011; Street et al., 2001; van den Broek et al., 1996; Vivier et al., 2011). During critical times, such as after surgery and during adjuvant treatment, women are at risk for post-surgical tumor dissemination and NKCA is more effective in halting nascent tumor cell seeding when tumor burden is low (Avraham and Ben-Eliyahu, 2007; Lutgendorf et al., 2007). Thus, greater and more prolonged reduction in NKCA may jeopardize cancer control.

Given that early life adverse experiences can shape future behavioral and immunological stress reactivity, the purpose of this study was to determine whether childhood adversity influences the intensity and duration of perceived stress, depressive symptoms, fatigue, quality of life, levels of circulating IL-6, as well as NKCA of women from breast cancer diagnosis through early survivorship. Most studies evaluating the effect of early life stress on adult outcomes have employed healthy or community samples and used cross sectional designs. Few studies have evaluated longitudinal effects of early life adversity in individuals facing the threat of serious illness. Such a determination may identify a potential vulnerability factor posited to contribute to a worse behavioral and immunological profile in women during breast cancer treatment, as well as during recovery from the cancer experience. This is significant given that a substantial number of women are at risk for more intense and/or prolonged behavioral symptoms and immune dysregulation, which would not only diminish quality of life, but may also reduce effectiveness of immune-based cancer control mechanisms.

2. Methods

2.1. Participants and procedure

Women with early stage breast cancer were enrolled from the breast oncology clinics of three medical centers located in the west-suburban Chicago metropolitan area. Eligible women were identified after completion of their breast surgery and when their full surgical pathology report was available. Women were excluded if diagnosed with recurrent breast cancer or other cancers, immune-based or inflammatory disease, major psychiatric disorder or cognitive dysfunction. They were also excluded if they were substance abusers, used tobacco products, were taking corticosteriods, or if they were to receive systemic chemotherapy as part of their cancer treatment plan. Forty women were enrolled from participating breast oncology clinics; 34 were treated with breast conserving surgery followed by radiation therapy, while 6 women were treated with surgery only and no adjuvant radiation therapy. Participating women were evaluated five times, spanning a period of nine months. T1 evaluations occurred at least 2 weeks after surgery to allow dissipation of effects of anesthesia and surgical stress; on average T1 occurred 7 ± 5 weeks after surgery. With re-

spect to T1, subsequent evaluations were T2 = 5 ± 2 weeks, T3 = 9 ± 2 weeks, T4 = 15 ± 3 weeks, T5 = 34 ± 3 weeks. Participants completed instruments for perceived stress, depressive mood, fatigue and quality of life at each assessment; whereas, childhood adversity was measured once. For each assessment, venipuncture for blood sample procurement was accomplished in the morning between 6:30 and 11:30 AM. Blood specimens were used for determination of NKCA and measurement of circulating IL-6 levels. This study was approved by the Institutional Review Boards for the Protection of Human Subjects of all participating sites and informed consent was obtained from all participants.

2.2. Psychometric instruments

2.2.1. Childhood trauma questionnaire (CTQ)

To assess childhood adversity, the CTQ-Version 3 was administered. This instrument measures the nature and extent of exposure to childhood trauma/maltreatment. The CTQ assesses five domains of maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect) and the rate of occurrence of each item on a 5-point scale from 'Never True' to 'Very Often True'. The CTQ has demonstrated excellent test–retest reliability (Bernstein et al., 1994) and good convergent validity, as it correlated highly with interview-based rating of childhood abuse, as well as with therapists' ratings of abuse (Bernstein et al., 1994).

2.2.2. Perceived stress scale (PSS)

Perception of stress was measured using the PSS, a brief 10-item scale that assesses the degree to which life experiences are appraised as uncontrollable. It is a widely used measure of general perceived stress (Cohen et al., 1983). Reliability (stability) is 0.85 and Cronbach alphas range from 0.75 to 0.86 (Cohen and Williamson, 1988).

2.2.3. Center for epidemiologic studies, depression scale (CES-D)

Depressive symptoms were measured using the CES-D, which is a 20-item tool that assesses the frequency and duration of depressive symptoms (Radloff, 1977). It has been used widely in cancer studies. Scores range from 0 to 60 and a score of greater than 16 indicates risk for clinical depression. The CES-D has good construct validity in clinical and community samples, good test–retest reliability and an internal consistency alpha of .86 (Radloff, 1977).

2.2.4. Multidimensional fatigue scale inventory

To capture the multidimensional nature of cancer-related fatigue, fatigue was measured over the past month using the Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF) (Pickard-Holley, 1991; Stone et al., 1998). The MFSI-SF measures overall fatigue, as well as fatigue experienced in five domains (general, emotional, physical, mental, vigor). Factor analysis demonstrated good fit for the five factors. Internal consistency ranges from 0.87 to 0.96 (Stein et al., 2004).

2.2.5. Quality of life index

Quality of life was defined as "a person's sense of well-being that stems from satisfaction or dissatisfaction with the areas of life that are important to him/her" and was assessed using the Ferrans Quality of Life Index (QLI) (Ferrans, 1990). QLI measures life satisfaction in four domains: health/functioning, socioeconomic, psychological/spiritual, and family. Two parts evaluate 34 items on a 6-point scale. Part I measures satisfaction within each domain. Part II measures perceived importance of each item. Satisfaction scores are weighted by importance. QLI has been used in many breast cancer studies and QLI demonstrates good content and construct validity (Ferrans and Powers, 1985). The Cronbach alpha for breast cancer patients ranges from 0.93 to 0.96 (Ferrans, 1990; Hughes, 1993), while criterion validity is 0.80 (Ferrans, 1990) and test–retest reliability is 0.87 (Ferrans and Powers, 1985).

2.2.6. Demographic and medical history

Demographic information, including age, race, marital status, education, and employment status, was obtained using a self-report questionnaire. Cancer pathology, staging, and cancer treatment were validated by medical records. Information regarding presence of other comorbidities and use of medications was collected by self-report. A weighted index of comorbid disease was calculated (Charlson et al., 1987) and used to control for co-morbidities in the statistical analyses.

2.3. Immunological measures

2.3.1. Isolation of peripheral blood mononuclear cells

Blood was collected in sterile heparinized tubes and processed immediately. Heparinized peripheral blood was overlaid onto Ficoll/Hypaque and centrifuged at 1000*g* for 20 min. The peripheral blood mononuclear cells (PBMC) at the interface were washed twice with Hank's balanced salt solution prior to assessment of NKCA. The PBMC subsets were determined as described previously (Witek-Janusek et al., 2007) and did not change across assessment periods (i.e. T1–T5).

2.3.2. NKCA

Natural killer cell lytic activity against tumor targets was assessed using PBMC in a standard chromium release assay, as previously described (Witek-Janusek et al., 2007). K562 tumor cells were radioactively labeled with 100 uCi of [^{51}Cr] (New England Nuclear, Boston, MA). Radiolabeled K562 cells were incubated for 4 h with PBMC. Following incubation, the supernatants were removed using a Skatron harvesting press (Skatron Inc., Sterling, VA) and the associated radioactivity was determined. Effector to target ratios for NKCA was 50, 25, 12, and 6:1. Results are expressed as % cytotoxicity and calculated by the formula:

$$\%\ \text{Cytotoxicity} = \frac{(\text{experimental DPM}^{*}) - (\text{minimum DPM})\leftarrow}{(\text{maximum DPM}) - (\text{minimum DPM})\leftarrow} \times 100.$$

All experimental means were calculated from triplicate values. Lytic units (LU) were calculated by a program written by David Coggins, FCRC, Frederick, MD and represent the number of cells per 10^7 effectors required to achieve 20% lysis of the targets. *DPM = disintegrations per minute.

2.3.3. Plasma IL-6

Enzyme linked immunoabsorbent assay (ELISA) was used to measure circulating IL-6 in plasma samples (R & D Systems, Minneapolis MN). All samples were analyzed in duplicate. Sensitivity was <7 pg/ml and intra assay variability was <7%.

2.4. Statistical analysis.

Preliminary analyses were carried out using SPSS 17.0. Summary descriptive statistics for all outcome and predictor variables were calculated and all variables were examined for normality of distribution. Values for IL-6 were log transformed, as these were not normally distributed. Bivariate correlations among the scales from the Childhood Trauma Questionnaire (i.e. physical abuse, physical neglect, emotional abuse, and emotional neglect) were conducted. There was a strong positive association between the emotional abuse and the emotional neglect scales ($r = 0.90$, $p < 0001$). In order to avoid multicollinearity effects in the subsequent multilevel regression models, the scores on these two scales were combined into one index, termed as emotional neglect/abuse.

Physical abuse and physical neglect scales were moderately correlated (*r*s = 0.30–42) and were treated as separate predictor variables. The sexual abuse scale was not included in the final analysis because only three participants reported "*rarely true*" for one or more questions regarding their history of sexual abuse. Hence, three childhood adversity factors were evaluated in the final analysis: physical abuse, physical neglect, and emotional neglect/abuse.

HLM 6.08 software for computing multilevel model for change (Raudenbush and Bryk, 2002), based on full maximum likelihood estimation, was used to examine intra-individual and inter-individual differences in initial status and trajectories of change over time in depressive symptoms, perceived stress, fatigue, quality of life, plasma IL-6, and NKCA. Unlike the traditional analysis of variance for repeated measures, HLM estimates change for each individual and not merely change in group trends across time (Hedeker, 2004). Such an approach allows for individual-specific effects to be included in the model to capture the heterogeneity among participants in both the initial level and growth over time. Importantly, HLM treats time as a continuous variable letting each participant have her own data collection schedule. Another advantage of the multilevel approach is that it allows for the analysis of participants with incomplete and unbalanced data across time points, resulting in increased statistical power and less biased findings (Hedeker, 2004). HLM also estimates variance components associated with the initial level and the time trend, which is indicative of the sample's heterogeneity.

With HLM of longitudinal data, the outcome variables (i.e. depressive symptoms, fatigue, perceived stress, quality of life, IL-6, and NKCA) are conceptualized to be nested within individuals and the growth modeling of change in these variables has two levels. At Level 1, the outcome variable is a function of person-specific parameters (i.e. initial level and time trend) plus error. At Level 2, the subject's intercept and slope are modeled as a function of the predictor variables that vary between participants (i.e. childhood trauma questionnaire scales), plus an error associated with each individual for each parameter. Combination of these two levels results in a mixed model with fixed and random effects (Raudenbush and Bryk, 2002).

The HLM analysis for each of the outcome variables was performed in three stages. First, in order to investigate intra-individual variability over time, an unconditional model (i.e. model with no covariates) was fit to the data. This stage examined how depressive symptoms, perceived stress, fatigue, quality of life, and NKCA changed from the time of the first assessment to approximately nine months later. Importantly, the variance components were estimated to evaluate individual variation around the sample-wide model estimates. Time was measured in weeks from T1, which was coded as zero. The slope coefficients are interpreted as change per each additional week from T1. Both linear and quadratic trends were examined and goodness-of-fit tests of the deviance between linear and quadratic models were used to assess the most appropriate fit.

The second stage of HLM analysis examined the potential effects of the following variables: demographic (age, race, education, marital status and BMI for IL-6), co-morbidities, categories of medication usage (statin agents, beta blockers, agents directed at the renninangiotensin system, anti-depressants, and oral hypoglycemic agents), and cancer treatment variables (cancer stage, type of surgery, radiation therapy, time since surgery, and hormonal treatment for cancer, i.e. tamoxifen and aromatase inhibitors). In addition, for women receiving radiation therapy, initial values of outcomes were evaluated with respect to number of radiation treatments received.

Lastly, the effect of the percentage of NK cells ($CD56^+$) was examined with respect to NKCA. Only variables that had a significant effect (*t*-value above 2.00) were included in the third stage of analysis, and only those that retained their significance in combination with other predictor variables were left in the final model. Lastly, during the third stage, potential moderating effects of the childhood adversity factors (physical abuse, physical neglect, emotional neglect/abuse) were examined. Childhood adversity factors were time-invariant predictors (assessed at T1 only) and were entered into the models simultaneously as continuous variables.

3. Results

3.1. Descriptive characteristics of participants

Forty women were enrolled and evaluated longitudinally at five distinct times (T1–T5). Missing data was minimal. For psychological data only one subject did not complete the CES-D and the QLI at T3. For NKCA, 40 subjects provided adequate blood samples for evaluation of NKCA at T1, while 37, 38, 37, and 37 subjects had NKCA evaluations at T2 through T5, respectively. For circulating IL-6, plasma samples from 40 subjects were evaluated at T1, while 38, 38, 36, and 38 samples were evaluated at T2 through T5, respectively. Reasons for missing immune data were inadequate specimen blood volume, inability to perform venipuncture, or frank refusal of venipuncture.

Demographic, disease, and treatment characteristics of the participants are summarized in Table 1. Women were predominantly Caucasian (84%), married (71%), and well educated (*M* = 15.4 years, SD = 2.8). The majority of women had Stage 0 or Stage I breast cancer (78%). All women underwent surgery for removal of their cancer (31 had breast conserving surgery and 9 women had a mastectomy). Thirty-four women received radiation therapy after their surgery and 10 of these women were also placed on hormonal therapy (tamoxifen or an aromatase inhibitor), as part of their cancer treatment. The remaining 6 women were treated with surgery only. See Table 1. The most prevalent medications used by women in this sample were statin agents (*N* = 9), followed by beta blockers (*N* = 6) and agents directed at the rennin-angiotensin system (*N* = 6). Two women used oral hypoglycemic agents and three women used anti-depressants.

Table 1
Demographic characteristics (*N* = 40).

Age (years) mean ± SD	55. 6 ± 9.4
Education (years) mean ± SD	15.4 ± 2.8
	Frequency
Race	
Caucasian	33
African American	4
Hispanic	1
PI/Asian	2
Marital Status	
Married	29
Divorced/separated	6
Single	5
Income	
$10,000–29,000	6
$30,000–59,000	6
$60,000 and higher	28
Stage of cancer	
Stage 0	12
Stage I	21
Stage IIA	7
Treatment[a]	
Surgery only	6
Surgery + radiation therapy	24
Surgery + radiation + hormonal therapy	10
Surgery Type	
Breast conserving	31
Mastectomy	9

SD = standard deviation.
[a] Some women received multiple forms of therapy.

Descriptive data (means and standard deviations) for all behavioral and immune measures for the five evaluation periods, as well as the summary statistics for the CTQ subscales are provided in Table 2. For women in our sample, the means and standard deviations for the CTQ scales are similar to that reported for a large validation sample of healthy US adult women (Scher et al., 2001). Overall, average values for depressive symptoms, perceived stress and fatigue declined from T1 to T5, while quality of life increased throughout the same time period. NKCA reached a nadir at T2 and showed a continual increase from T3–T5. NK cell percentages remained stable over time. Average values of NKCA at T5 are similar to normative values for healthy women, as previously reported from our laboratory (Witek-Janusek et al., 2008, 2007). Average levels of circulating IL-6 essentially remained the same throughout the assessment period. Of note, no group differences were found ($t(38) = 0.98$, $p = 0.33$) in the initial level of IL-6 and NKCA between women who received radiation therapy and women who did not. Also, no association was observed between the time since surgery and the baseline levels of IL-6 ($r = -0.26$, $p = 0.15$) and NKCA ($r = 0.04$, $p = 0.78$).

3.2. Unconditional effects of time: intra-individual variation

Estimates of fixed and random effects of the unconditional (i.e. no covariates) model are presented in Table 3. The unconditional effects of time for all outcome measures are illustrated in Fig. 1. The mean scores for the outcome variables depicted in the figures are estimated or predicted by the HLM results.

3.2.1. Depressive symptoms (CES-D)

Goodness-of-fit tests of the deviance indicated that a linear model fit the data better than did a quadratic model ($p < 0.01$). Estimates of fixed and random effects of the unconditional (i.e. no covariates) model for CES-D scores are presented in Table 3. The sample as a whole demonstrated a significant decrease in the level of depressive mood over the 9 months of the study ($b = -0.07$, $SE = 0.03$, $p = 0.04$). The average initial estimated level of depressive symptoms at diagnosis was 12.5 (SE = 1.25), which is below the established score of 16 indicative of elevated risk for clinical depression (Radloff, 1977). However, random effects indicated that women exhibited significant heterogeneity in the extent of depressive mood at diagnosis ($p < 0.0001$), but not in their trajectories over time. See Fig. 1a and Table 3.

3.2.2. Perceived stress (PSS)

Assessed by the goodness-of-fit test of the deviance scores, a quadratic trend was found to more adequately capture the change in the level of perceived stress ($p < 0.05$). As shown in Table 3, the average initial level of perceived stress was estimated to be 17.5 ($SE = 0.98$). This level is elevated as compared to a community sample of US adults (PSS mean = 13.0, SD = 6.1; (Cohen and Williamson, 1998), indicating that women were experiencing high perceived stress at the time of their enrollment. Both the estimated linear ($b = -0.29$, $SE = 0.10$, $p < 0.001$) and quadratic rate of change per week ($b = 0.006$, $SE = 0.002$, $p < 0.01$) were significant. The linear slope represents instantaneous rate of change at a specific moment and the quadratic slope defines the curvature of the slope (Singer and Willett, 2003). The overall trajectory is defined by the weighted combination of linear and quadratic growth factors (see Fig. 1b). The heterogeneity in individual change parameters, estimated by the variance components, indicated that there was significant variation in the initial level as well as the trajectories of perceived stress between women (p values <0.0001).

3.2.3. Fatigue (MFSI)

A quadratic model fit the data significantly better ($p > 0.05$). As shown in Table 3, on average women were estimated to have elevated levels of fatigue (Stein et al., 1998) at time of the first evaluation, 14.3 ($SE = 2.5$). A significant linear ($b = -0.6$, $SE = 0.23$, $p = 0.01$) and quadratic ($b = 0.014$, $SE = 0.007$, $p = 0.04$) change in fatigue were also observed, with average levels of fatigue decreasing most precipitously from initial levels through T4 (Fig. 1c). The variance components of the model indicated that there was a significant variation in the reports of fatigue at diagnosis and trajectories over the nine months (p values <0.001).

3.2.4. Quality of life (QLI)

A linear trend fit the data significantly better ($p < 0.001$). As shown in Table 3, initial levels of quality of life were estimated at 21.5 ($SE = 0.70$). As illustrated in Fig. 1d, on average, quality of life was estimated to improve over the nine months of the study ($b = 0.07$, $SE = 0.025$, $p = 0.01$). Similar to previous models, there was heterogeneity in the reports at diagnosis, as well as in the change over time, indicated by the variance components of the model (p values <0.001).

Table 2
Descriptive data for psychological and immune variables.

	T1		T2		T3		T4		T5	
	M	SD	M	SD	M	SD	M	SD	M	SD
CESD	12.9	10.3	12.6	10.8	10.9	8.7	10.9	9.9	10.5	9.3
PSS	16.9	7.2	16.1	7.3	15.1	6.4	15.1	7.2	15.0	7.1
MFSI	12.7	10.1	12.2	23.6	9.9	20.9	7.9	19.9	11.3	25.5
QLI	21.1	4.6	21.1	4.7	22.0	4.7	22.4	4.7	23.1	5.9
NKCA	70.5	46.9	57.2	43.8	63.7	48.4	75.8	56.9	90.1	66.7
NK cells	13.9	7.6	13.7	8.6	13.7	6.4	12.0	6.29	14.1	7.1
IL-6 (pg/ml)	1.2	0.8	0.8	0.4	0.9	0.6	1.0	0.5	1.0	0.8
IL-6 (log)	−0.02	0.3	−0.16	0.2	−0.09	0.3	−0.06	0.2	−0.08	0.3
CTQ scales										
Physical neglect					6.6				2.6	
Emotional neglect					9.2				4.9	
Emotional abuse					8.9				4.9	
Physical abuse					6.9				4.3	
Sexual abuse					6.8				3.4	
Emotional neglect/abuse					9.1				4.8	

Values are mean (M) and standard deviation (SD). CESD = Center for Epidemiologic Studies Depression Scale, PSS = Perceived Stress Scale; MFSI = Multidimensional Fatigue Symptom Inventory, QLI = Quality of Life Index, CTQ = Childhood Trauma Questionnaire, NKCA = Natural Killer Cell Activity (lytic units 20%), NK cells = percentage of $NK56^+$ cells in peripheral blood, IL-6 is pg/ml of plasma. The initial evaluation (T1) occurred 7 ± 5 weeks post surgery, and with respect to T1, subsequent evaluations were T2 = 5 ± 2 weeks, T3 = 9 ± 2 weeks, T4 = 15 ± 3 weeks, T5 = 34 ± 3 weeks.

Table 3
Unconditional and final hierarchical linear models for psychological and immune outcomes.

	CESD	PSS	MFSI	QLI	NKCA	IL-6 (log)
Unstandardized coefficients (SE)						
Fixed effects: intercept	12.55 (1.25)[b]	17.48 (.98) [b]	14.26 (2.5) [b]	21.51 (.70) [b]	70.51 (7.18) [b]	−.082 (.035) [c]
Time[a] (linear)	−.07 (.03)	−.29 (.10) [c]	−.60 (.23) [c]	.07 (.025) [c]	.55 (.41)	−.00007 (.0012)
Time[2] (quadratic)	–	.006 (.002) [d]	.014 (.007) [d]	–	–	–
Random effects: intercept	79.06[b]	48.25[b]	311.91[b]	18.47[b]	1531.94[b]	.037
Time (linear)	.012	.37[b]	1.17[b]	.018[b]	3.95[b]	.0008[d]
Time[2] (quadratic)	–	.0002[b]	.0011[b]	–	–	–
Fixed effects: baseline						
Intercept	12.16 (1.25)	16.87 (.92)	13.32 (2.62)	21.48 (.52)	70.28 (5.67)	−.082 (.03)
Age	–	−.22 (.06) [d]	−1.04 (.31) [c]	–	–	–
BMI	–	–	–	–	–	.019 (.004) [b]
Radiation start[e]	6.24(2.89) [d]	–	–	–	–	–
Physical abuse	−1.57 (.51) [c]	−1.01 (.72)	−1.09 (1.16)	.66 (.21)	.14 (1.83)	.013 (.01)
Physical neglect	.33 (.67)	−.71 (.49)	1.07 (1.40)	−.24 (.21)	4.17 (3.21)	−.013 (.012)
Emotional neg/abuse	1.21 (.38) [c]	1.20 (.28) [b]	1.61 (.79) [d]	−.69 (.16) [b]	−2.68 (1.20) [c]	−.01 (.007)
Time slope (linear)						
Intercept	−.06 (.04)	−.26 (.11)	−.75 (.25)	.07 (.02)	.73 (.35)	−.00003 (.0011)
NK cells	–	–	–	–	3.55 (.84) [b]	–
Physical abuse	.006 (.018)	−.04 (.04)	−.03 (.10)	.004 (.008)	−.12 (.13)	−.0009 (.0007)
Physical neglect	.011 (.021)	.23 (.06) [b]	.15 (.14)	−.014 (.007) [d]	.15 (.16)	.0009 (.0003) [d]
Emotional neg/abuse	−.022 (.06)	−.06 (.04)	.017 (.07)	.006 (.004)	−.04 (.09)	.0004 (.0003)
Time slope (quadratic)						
Intercept	–	.006 (.003)	.016 (.008)	–	–	–
Physical abuse	–	.001 (.001)	.002 (.003)	–	–	
Physical neglect	–	−.005 (.001) [c]	−.003 (.004)	–	–	
Emotional neg/abuse	–	.001 (.0009)	−.001 (.002)	–	–	
Random effects: intercept	48.24[b]	26.51[b]	236.80[b]	11.17[b]	809.30[c]	.0243[b]
Slope (linear)	.013	.21[d]	.91[d]	.016[b]	4.74[b]	.00001
Slope (quadratic)	–	.0001[d]	.0009[d]	–	–	–
NK cells	–	–	–	–	9.56	–

Abbreviations: CESD = Center for Epidemiologic Studies Depression Scale, MFSI = Multidimensional Fatigue Scale Index, PSS = Perceived Stress Scale, QLI = Quality of Life Index, NKCA = Natural Killer Cell Activity Lytic Units 20%, NK cells = percentage of $CD56^+$ cells in peripheral blood, BMI = body mass index; SE = Standard Error of the coefficient; IL-6 is pg/ml of plasma.

[a] Time was coded 0 at the first assessment visit.
[b] $P < 0.001$.
[c] $P < .01$.
[d] $P \leqslant .05$.
[e] Procurement of T1 data with respect to radiation start date.
[2] Refers to the quadratic rate of change.

3.2.5. NKCA

Overall NKCA demonstrated a linear increase in trajectory from the initial evaluation, which was estimated at 70.5 lytic units ($SE = 7.18$). On average, NKCA was estimated to improve over the course of the study, with the rate coefficient approaching significance ($b = 0.55$, $SE = 0.29$, $p = 0.06$). The variance components indicated significant inter-individual differences among women in NKCA at initial assessment and in change over the course of the study ($p < 0.0001$). See Table 3 and Fig. 1e.

3.2.6. Plasma IL-6

A linear model provided a significantly better fit for the data ($p < 0.05$). Although, the level of IL-6 did not change significantly over time for the sample as a whole ($b = -0.00007$, $SE = 0.0012$, $p = 0.89$), a significant amount of heterogeneity was observed for the initial status ($p < 0.001$) and slope ($p = 0.05$). See Table 3 and Fig. 1f.

3.3. Effects of childhood adversity: inter-individual variation

Childhood adversity factors (i.e. physical neglect, physical abuse, emotional neglect/abuse) and demographic characteristics were entered into the models to understand how these factors affect the pattern of change in depressive mood, perceived stress, fatigue, quality of life, and immune function (NKCA and IL-6) from diagnosis through early survivorship. In order to aid the interpretation of the fixed effects, predictor variables were grand-mean centered (i.e. the variable's sample mean was subtracted from each observation). As previously described, demographic and treatment variables were entered into the model separately. To achieve a parsimonious model, only those variables that retained their significance in combination with other co-variables and childhood adversity factors remained in the final model.

Results revealed that there was no effect of treatment variables (radiation therapy, type of surgery, time since surgery, and use of hormonal treatment for cancer therapy) on any study outcome. As well there was no effect of co-morbidities or medication usage, based on major categories of drugs used by women in this sample (i.e. statins, beta blockers, rennin-angiotensin blockers, antidepressants, or oral hypoglycemics). At initial assessment (T1), the timing of radiation significantly affected depressive symptoms but did not affect any other outcome measures. The effect of radiation timing on depression retained its significance when entered in combination with the childhood adversity factors; thus, timing of radiation was subsequently controlled for in the final model.

No effect on study outcomes was found for demographic variables (education, race, marital status, and income) and these variables were omitted from the final models. Age was found to be significantly associated with stress and fatigue intercept parameters and retained significance when entered in combination with the childhood adversity factors; thus age was controlled in the final models. BMI was significantly associated with the plasma IL-6 intercept parameter. NKCA cell percentage was associated with NKCA. Thus, both BMI and NK cell percentage were controlled in the final models (see Table 3).

NK cell percentage is a time-variant variable and was entered into the Level 1 model. Childhood adversity variables were entered

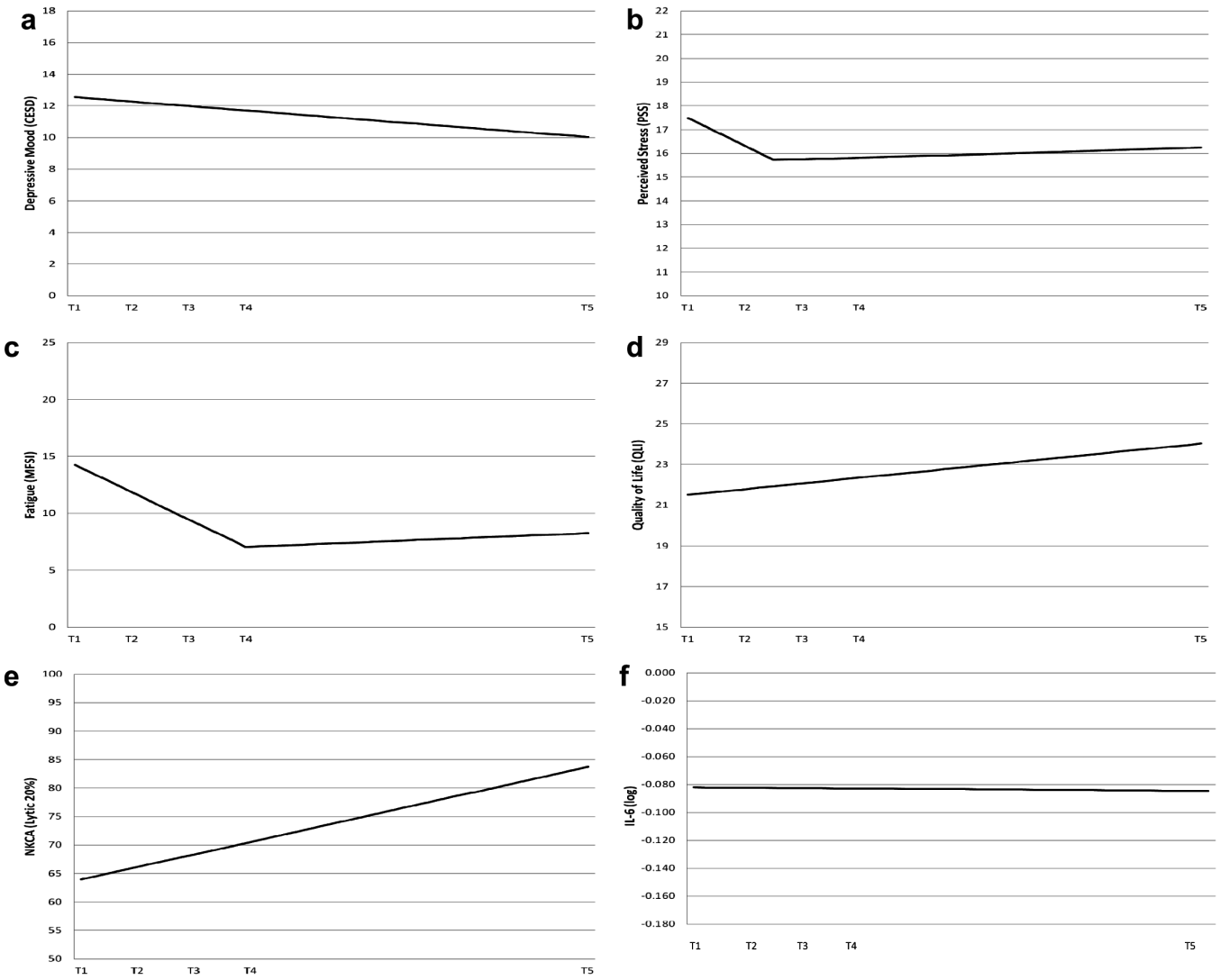

Fig. 1. Unconditional model estimates of the growth trajectories for (a) depressive symptoms, (b) perceives stress, (c) fatigue, (d) quality of life, (e) NKCA, and (f) plasma IL-6. Graphical representation of the unconditional effect of time on depressive mood (CESD scores), perceived stress (PSS scores), fatigue (MFSI scores), quality of life (QLI scores), natural killer cell activity (NKCA; lytic units 20%), and circulating level of IL-6. The initial evaluation (T1) occurred 7 ± 5 weeks post surgery, and with respect to T1, subsequent evaluations were T2 = 5 ± 2 weeks, T3 = 9 ± 2 weeks, T4 = 15 ± 3 weeks, T5 = 34 ± 3 weeks.

simultaneously into the HLMs. Figs. 2 and 3 illustrate the effects of these predictors on the trajectories of behavioral and immune outcome measures. The change curves for psychological and immune measures were based on differences in exposure to childhood emotional neglect/abuse (Fig. 2) and exposure to childhood physical neglect (Fig. 3). This was calculated as the average upper (i.e. high neglect/abuse) and the average lower quartiles (i.e. low neglect/abuse), and is illustrated in this manner.

3.3.1. Depressive symptoms

As shown in Table 3 and Fig. 2a, childhood emotional neglect/abuse ($b = 1.21$, $SE = 0.35$, $p = 0.003$) was a significant predictor of the initial level of depressive symptoms. Women who reported greater levels of childhood emotional neglect/abuse were estimated to have greater levels of depressive symptoms, which remained greater over the time evaluated. Childhood physical abuse was negatively related to the initial levels of depressive symptoms ($b = -1.57$, $SE = 0.39$, $p = 0.001$). None of the childhood adversity factors were associated with a change in the linear slope for depressive symptoms. See Table 3.

3.3.2. Perceived stress

Similarly, childhood emotional neglect/abuse was significantly associated with the initial level of perceived stress ($b = 1.20$, $SE = 0.28$, $p < 0.001$). See Table 3. Women who reported greater levels of childhood emotional neglect/abuse were estimated to have higher perceived stress at initial assessment, and these levels remained higher over the time evaluated (Fig. 2b). Age was also a significant predictor of the intercept, such that younger women were estimated to have lower initial levels of perceived stress ($b = -0.22$, $SE = 0.06$, $p = 0.02$). Further, as shown in Table 3, childhood physical neglect was a significant predictor of the estimated linear ($b = 0.23$, $SE = 0.06$, $p < 0.001$) and quadratic ($b = -0.005$, $SE = 0.001$, $p = 0.004$) trends, but was not associated with the initial level of perceived stress ($p = 0.15$). As illustrated in Fig. 3a, although all women initially reported similar elevations in the level of perceived stress, for those women who reported higher levels of childhood physical neglect, perceived stress continued to remain elevated over time. In contrast, for women with lower levels of childhood physical neglect, perceived stress declined over the first 16 weeks and slightly increased thereafter. No significant association between

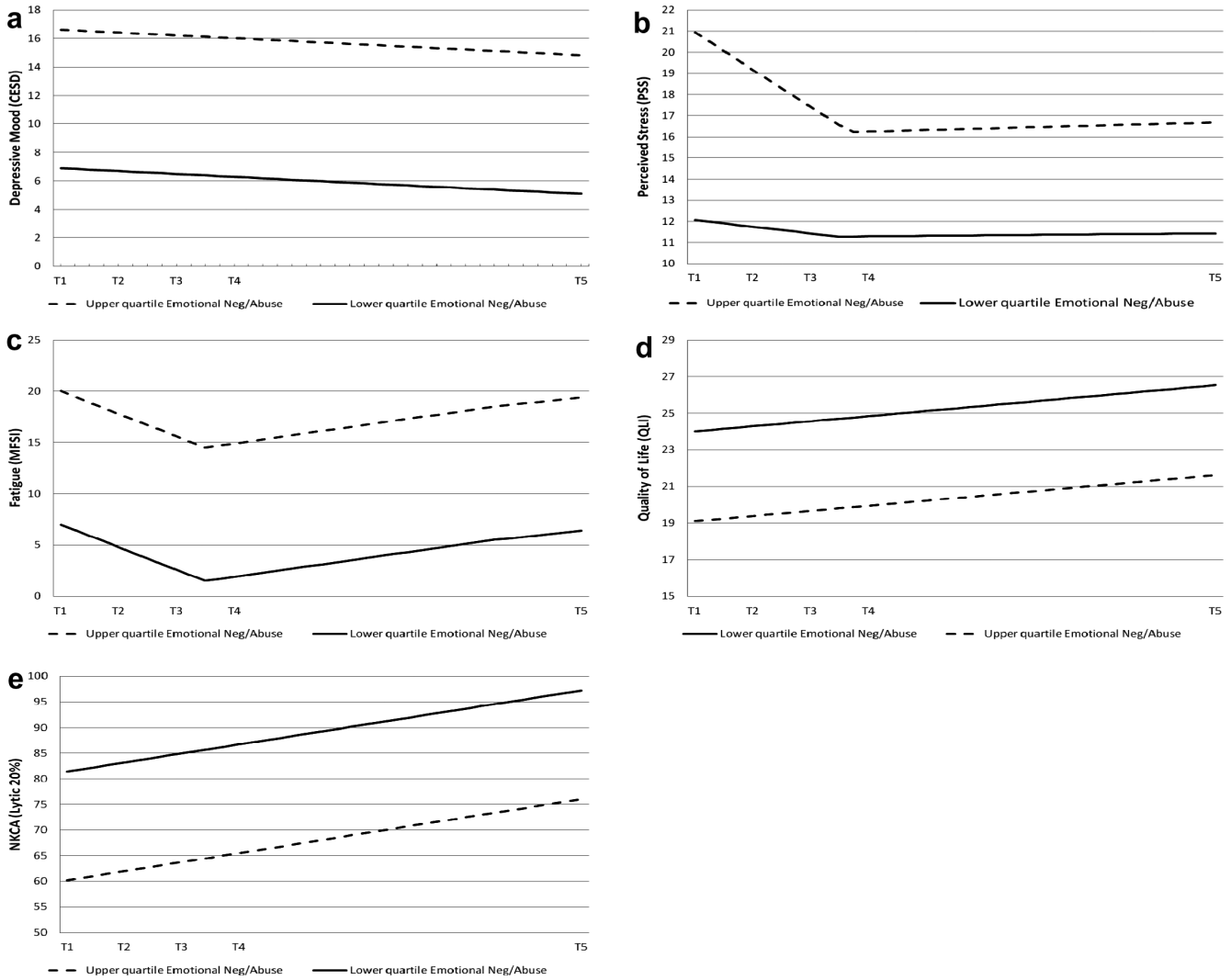

Fig. 2. Effect of emotional neglect/abuse on (a) depressive mood, (b) perceived stress, (c) fatigue, (d) quality of life, (e) NKCA. Graphical representation of the relationship between childhood emotional neglect/abuse (calculated as average upper/lower quartiles) and depressive mood (CESD scores), perceived stress (PSS scores), fatigue (MFSI scores), quality of life (QLI scores), and natural killer cell activity (NKCA; lytic units 20%). Graphs are estimated by the hierarchical linear models from the time of the initial assessment (T1) through an approximate 9-month period (T5). Women who reported greater levels of childhood neglect/abuse were estimated to have more depressive mood (b = 1.29, $p = .002$), greater perceived stress (b = 1.20, $p < .001$), more fatigue (b = .66, $p = .04$), poorer quality of life (b = -.69, $p < .001$), lower NKCA (b = -3.12, $p = .01$) at the initial assessment and through the 9-month study period. The initial evaluation (T1) occurred 7 ± 5 weeks post surgery, and with respect to T1, subsequent evaluations were T2 = 5 ± 2 weeks, T3 = 9 ± 2 weeks, T4 = 15 ± 3 weeks, T5 = 34 ± 3 weeks.

childhood physical abuse and perceived stress was observed for either the intercept or linear/quadratic slopes.

3.3.3. Fatigue

Childhood emotional neglect/abuse was a significant predictor of the initial level of fatigue ($b = 1.61$, $SE = 0.79$, $p = 0.04$) but was not associated with linear or quadratic change in fatigue over time. As illustrated, women who reported greater childhood emotional neglect/abuse were estimated to have higher levels of fatigue at initial assessment and their fatigue levels remained higher over time (see Fig. 2c). Age was also associated with the initial level of fatigue, with younger women reporting greater levels of fatigue ($b = -1.04$, $SE = 0.31$, $p = 0.004$). None of the childhood adversity factors were associated with the pattern of change (i.e. trajectory) in fatigue (Table 3).

3.3.4. Quality of life

Childhood emotional neglect/abuse was a significant predictor of the initial level of quality of life ($b = -0.69$, $SE = 0.16$, $p < 0.001$), but was not associated with the linear slope ($p = 0.20$). Women who reported higher levels of childhood emotional neglect/abuse were estimated to report lower quality of life and this pattern remained over the course of the 9 month period (Fig. 2d). Physical neglect or physical abuse during childhood was not associated with the initial level of quality of life. However, an association between the linear change in quality of life and childhood physical neglect approached significance ($b = -0.014$, $SE = 0.007$, $p = 0.06$). This is illustrated, in Fig. 3b, which shows that women who reported lower levels of physical neglect exhibited a faster rate of improvement in quality of life compared to women who had greater physical neglect. See Table 3 and Fig. 3b.

3.3.5. NKCA

The initial level of NKCA was significantly associated with childhood emotional neglect/abuse ($b = -2.68$, $SE = 1.20$, $p < 0.05$), in that women who reported greater levels of childhood emotional neglect/abuse were estimated to have lower NKCA at their first assessment. See Table 3 and Fig. 2e. NKCA increased over time

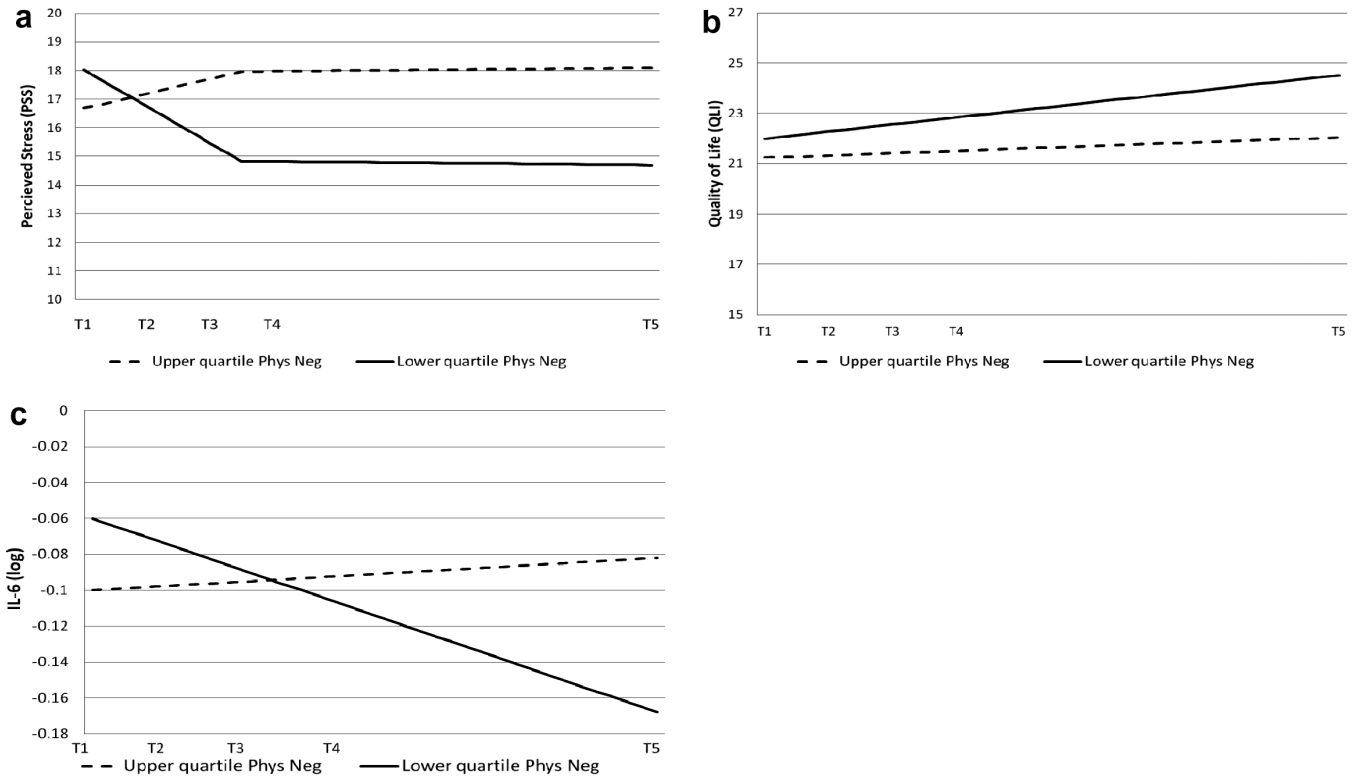

Fig. 3. Effect of physical neglect on (a) perceived stress and (b) quality of life, and (c) plasma IL-6. Graphical representation of the relationship between childhood physical neglect (calculated as average upper/lower quartiles) and perceived stress (PSS scores), quality of life (QLI scores), and circulating IL-6 level. Graphs are estimated by the hierarchical linear models from the time of the initial assessment (T1) through an approximate 9-month period (T5). At the initial assessment, there were no significant differences in perceived stress, quality of life, or plasma IL-6 between the women. However, those women who reported greater level of childhood physical neglect were estimated to have an increase in perceived stress (b = .23, $p < .001$; b quadratic = -.005, $p = .004$) over the first 16 weeks that remained elevated thereafter. Lower level of physical neglect was associated with faster improvement rate in quality of life (b = -.014, $p = .06$) and a greater decline in circulating IL-6 (b = .0009, $p = .03$). The initial evaluation (T1) occurred 7 ± 5 weeks post surgery, and with respect to T1, subsequent evaluations were T2 = 5 ± 2 weeks, T3 = 9 ± 2 weeks, T4 = 15 ± 3 weeks, T5 = 34 ± 3 weeks.

but the linear slope was not affected by childhood emotional neglect/abuse ($p > 0.05$). As a result of the lower initial levels of NKCA and the lack of the interaction between rate of change and childhood emotional neglect/abuse, women with greater childhood emotional neglect/abuse had lower NKCA for the duration of the study. For other childhood adversity factors (physical abuse and neglect), no associations with NKCA were observed for either the initial level or the linear slope (p values >0.05).

3.3.6. Plasma IL-6

Childhood physical neglect was a significant predictor of the linear slope ($b = .0009$, $SE = .0003$, $p = .03$), but not the initial level ($p = .31$) of plasma IL-6. These results indicate that although all women as a group initially have similar levels of circulating IL-6, those women who reported lower levels of physical neglect during their childhood exhibited a more precipitous decrease of IL-6 during the course of the study (Fig. 3c). In contrast, circulating IL-6 levels increased slightly, for women who reported greater childhood physical neglect. Other childhood adversity factors (physical abuse and emotional neglect/abuse) were not associated with IL-6 (Table 3).

4. Discussion

The results of this study demonstrate childhood emotional neglect/abuse to predict greater perceived stress, fatigue, depressive symptoms, and poorer quality of life, as well as lower NKCA in women evaluated after their breast cancer surgery (i.e. initial assessment in this study). It is possible that these worse outcomes are related to enduring effects of childhood emotional neglect/abuse on stress response systems, which heighten reactivity to the stress-associated with breast cancer diagnosis and treatment. Yet because these women could not be evaluated prior to their breast cancer diagnosis, it is just as likely that they had pre-existing behavioral traits, which may have contributed to or accounted for the findings observed at initial assessment. However, the present results also show childhood physical neglect to predict worse trajectories for perceived stress, circulating IL-6 and quality of life in women with breast cancer. Those findings support the notion that these women were more susceptible to the challenges associated with breast cancer diagnosis and treatment. As such, childhood adversity emerges as a salient vulnerability factor for women with breast cancer, which may affect their recovery.

Although previous studies have described individual differences in the psychological adjustment and immune recovery after breast cancer (Dhruva et al., 2010; Dunn et al., 2011; Henselmans et al., 2010; Thornton et al., 2007), to our knowledge this is the first investigation to demonstrate early adverse experiences during childhood to influence behavioral and immune function in women with breast cancer. The occurrence of childhood adversity is not uncommon for women. Nearly 30% of the women in a community sample reported some form of childhood maltreatment (Scher et al., 2004). Women in our study reported means and standard deviations for the CTQ scales similar to that reported for a large validation sample of healthy US adult women (Scher et al., 2001). Even though women in our sample were largely well-educated, middle income women, childhood adversity still emerged as an important pre-existing risk factor for psychological morbidity

and dysregulated immune function. It is likely that more profound effects would be observed in women raised in an environment of social disadvantage (Carroll et al., 2011), emphasizing the need for health care providers to recognize this potential risk factor in cancer patients.

For most women breast cancer diagnosis and associated cancer treatment are accompanied by psychological distress. Over time most women successfully adapt and recover (Bárez et al., 2007; Stanton et al., 2005). Yet there is considerable individual difference in the trajectory of psychological distress following breast cancer diagnosis. A recent report identified four distinct trajectories of distress in the first year after breast cancer diagnosis: women with no distress (36%); women with distress during active treatment only, which dissipated by two months post-treatment (33%); women with distress that emerged during early survivorship (15%); and women with chronic distress (16%) (Henselmans et al., 2010). The present study showed that childhood emotional neglect/abuse predicted greater levels of perceived stress at initial assessment; whereas, physical neglect predicted a sustained trajectory of increasing perceived stress. Finding differential effects for childhood emotional versus physical neglect is not unexpected. Evidence from numerous studies Illustrate that the type of adversity (emotional, physical or sexual) shapes the nature of adult vulnerability, as well as relative risk for future psychopathology (Ford, 2010; Teicher et al., 2006).

Symptoms of depression can persist in approximately one-third of women in the first year after breast cancer diagnosis (Bower, 2008; Burgess et al., 2005; Miller et al., 2008), indicating individual susceptibility for depressive symptoms. Consistent with this, longitudinal studies identify unique trajectories of depressive symptoms in women with breast cancer (Deshields et al., 2006; Dunn et al., 2011). Deshields et al. identified five distinct subgroups of depression (using the CES-D) in women undergoing radiation therapy: Never depressed, recover, become depressed, stay depressed, and vacillate (Deshields et al., 2006). More recently, Dunn et al. characterized four distinct profiles of depressive symptoms, based on CES-D scores obtained prior to surgery and up to 6 months after surgery. The trajectory of these profiles was described as Low Decelerating (38.9%), Intermediate (45.2%), Late Accelerating (11.3%), and Parabolic (4.5%). In that study over 60% of women met criteria for clinically relevant depressive symptoms, with younger women being more susceptible (Dunn et al., 2011). Collectively, this literature emphasizes the magnitude of depression risk among women with breast cancer, as well as the individual nature of timing and duration of symptom expression. Our results add to this literature by identifying childhood emotional neglect/abuse as a pre-existing risk factor contributing to individual variation in the manifestation of depressive symptoms. This is clinically relevant, as depressive symptoms heighten risk for poor cancer treatment adherence (Lawrence et al., 2004).

Fatigue is commonly experienced by women with breast cancer, and, like depression, fatigue can persist beyond treatment (Bower et al., 2000). Cancer-related fatigue is more intense and enduring than fatigue resulting from inadequate sleep or physical exertion (Poulson, 2001) and leads to more profound impairments in quality of life (Bower, 2008; Curt, 2000). Thus, for women in this study, who were exposed to childhood adversity, the co-occurrence of depressive symptoms and fatigue likely synergize and compromise recovery of quality of life after breast cancer treatment. On average women in our sample report high levels of fatigue after surgery and during treatment, with MFSI scores approaching values established for clinically relevant fatigue (scores >5) (Liu et al., 2009; Stein et al., 1998). Over time we observed a decreasing pattern of fatigue with levels normalizing approximately 2–3 months after completion of radiation therapy. Childhood emotional neglect/abuse did not influence the pattern of change in fatigue; but predicted higher levels of fatigue at the initial assessment that continued to be higher over the time evaluated. Other longitudinal studies report individual variations in the experience of fatigue among women with breast cancer, and identify demographic, trait, and disease/treatment variables to influence levels of fatigue. Dhruva et al. measured morning and evening fatigue in women with breast cancer before, during and up to 2-months post radiation therapy. Their results showed that being younger, having greater sleep disturbance, and having higher trait anxiety predicted greater morning fatigue at baseline; whereas, advanced disease stage and more medical co-morbidities predicted worse trajectories of fatigue (Dhruva et al., 2010). In contrast, our findings show no effect of disease stage or cancer treatment on initial fatigue levels or the trajectory of fatigue. This is likely due to the more homogenous sample of women evaluated in our study, as none of the women received chemotherapy, while 55% of the women in the study by Dhruva et al. received chemotherapy, in addition to radiation therapy (Dhruva et al., 2010). Consistent with others (Dhruva et al., 2010; Knobf and Sun, 2005), we observed that younger women had higher initial levels of fatigue that persisted over time.

There is a growing literature demonstrating that adults who experienced childhood abuse or neglect exhibit heightened emotional responsiveness to future stress exposure, increasing their risk for mood and anxiety disorders (Green et al., 2010; McLaughlin et al., 2010b). Such enhanced emotional responsiveness to stress has been linked to greater autonomic nervous system and hypothalamic–pituitary–adrenocortical (HPA) axis reactivity to stress (Heim et al., 2008). Considerable evidence from animal models demonstrates that early life stress leads to persistent hyperactivity of brain corticotrophin releasing hormone (CRH) peptidergic systems, which is posited to sensitize the HPA axis to subsequent stress (Meaney, 2001). Consistent with these findings in animals, women exposed to childhood abuse, with or without depression, were found to produce a greater adrenocorticotropic hormone (ACTH) response to stress challenge, compared to control women and to depressed women without such abuse (Heim et al., 2001, 2000b). Moreover, a history of child abuse predicted elevations in cerebral spinal fluid levels of CRH (Heim et al., 2008). It is theorized that childhood adversity induces a neuro-biological vulnerability that predisposes for heightened stress reactivity. For women in our study, this may contribute to greater depressive symptoms and fatigue, two common co-occurring symptoms in women with breast cancer. This supposition is supported by recent findings that identify stress-induced neuroendocrine hormone elevations to serve as a common biological mechanism for the co-occurrence of depressive symptoms and fatigue in women with breast cancer (Thornton et al., 2010).

Childhood abuse or maltreatment can engender a proinflammatory phenotype that persists over the life span (Brydon et al., 2004; Carpenter et al., 2010; Danese et al., 2007; Pace et al., 2006). A large birth cohort study demonstrated maltreated children to exhibit a significant and graded increased risk for low grade inflammation, years later in adulthood (Danese et al., 2007). In contrast, greater maternal emotional warmth was shown to reduce production of the proinflammatory cytokine, IL-6 (Chen et al., 2010a). When subjected to acute laboratory-induced social evaluative stress, healthy adults who experienced childhood maltreatment were shown to mount a greater proinflammatory response than adults without early maltreatment (Carpenter et al., 2010). In our sample of women, mean levels of plasma IL-6 did not change over time; yet, we observed substantial heterogeneity in IL-6 levels between the women. This heterogeneity can be attributed in part to childhood adversity, as women in our study who reported greater childhood physical neglect, exhibited sustained elevations in IL-6, with a slightly increasing trajectory. This contrasted with the decreasing IL-6 trajectory for women with little or no childhood physical ne-

glect. Sustained elevations in IL-6 may contribute to greater risk for more prolonged inflammation-related behavioral symptoms (Bower, 2008; Miller et al., 2008). Substantial evidence demonstrates that circulating proinflammatory cytokines can signal the brain and generate behavioral symptoms (Dantzer and Kelley, 2007; Miller et al., 2008, 2009a; Raison et al., 2006). Upon accessing the brain, peripheral proinflammatory cytokines affect the availability of neurotransmitters relevant to behavior, as well as increase brain CRH production, a key regulator of the stress response that is also implicated in depressive and anxiety like behaviors (Owens and Nemeroff, 1991). Moreover, proinflammatory cytokines can directly affect brain activity in regions involved in mood and anxiety disorders (Capuron et al., 2005, 2007). Previous studies demonstrated that women diagnosed with breast cancer have increased production of proinflammatory cytokines (Bower, 2008; Witek-Janusek et al., 2008, 2007), with concomitant fatigue and depressive symptoms (Bower, 2008; Jehn et al., 2006; Miller et al., 2008; Schubert et al., 2007). It is possible that a proinflammatory phenotype, rooted in childhood adversity, contributes to more fatigue and depressive symptoms in women with breast cancer. Furthermore, sustained elevations in IL-6 may negatively impact cancer prognosis, as others show that circulating IL-6 is associated with worse survival (Knupfer and Preiss, 2007).

The psychological stress associated with breast cancer is accompanied by a reduction in NKCA toward tumor cells (Thornton et al., 2007; Varker et al., 2007; Witek-Janusek et al., 2008, 2007). However, considerable individual differences in the reduction in NKCA during diagnosis and treatment, as well as in the restoration of NKCA following cancer treatment are observed (Thornton et al., 2007). Our results show that group means for NKCA exhibit an increasing trajectory of NKCA with time. However NKCA does not recover to levels consistent with women without breast cancer until months after completion of cancer treatment (Witek-Janusek et al., 2007, 2008). We also observe considerable heterogeneity in individual levels of NKCA and show that a portion of this heterogeneity is related to childhood adversity. Childhood emotional neglect/abuse predicted lower NKCA at initial assessment, and although the trajectory in NKCA was not influenced by childhood adversity, NKCA remained lower for months after completion of cancer treatment for women with such adversity. NK cells are relevant to cancer control, protecting against tumor initiation, growth and metastasis in a variety of ways (Vivier et al., 2011). Higher levels of NKCA in cancer patients correlate with a better prognosis (Gonzales et al., 1998; Koda et al., 1997; Liljefors et al., 2003; Nakamura et al., 2000; Seo and Tokura, 1999; Taketomi et al., 1998); while impaired NKCA correlates with increased tumor invasiveness (Ishigami et al., 2000; Konjević et al., 2001; Levy et al., 1984; Takeuchi et al., 2001; Villegas et al., 2002). NK cells are especially important during critical times marked by risk for tumor dissemination, such as after surgery and during the early recovery phase after completion of adjuvant therapy (i.e. the period of time when women were evaluated in this study) (Avraham and Ben-Eliyahu, 2007; Ben-Eliyahu, 2003; Lutgendorf et al., 2007; Stojanovic and Cerwenka, 2011). Consequently, women with a history of childhood emotional neglect and abuse may be at greater risk for poor health outcomes resultant from reduced NKCA.

As noted, childhood adversity intensifies the inflammatory response to acute laboratory stress during adulthood (Brydon et al., 2004; Carpenter et al., 2010; Pace et al., 2006) and is associated with greater IL-6 and TNF-alpha levels in older adults experiencing chronic stress related to caregiving (Kiecolt-Glaser et al., 2010). However, to our knowledge the findings reported here are the first to demonstrate that early life adversity in humans not only results in a more persistent elevation of circulating IL-6, but also can predispose to lower levels of NKCA during the time period after surgery (i.e. initial assessment). These findings were observed in women experiencing a naturalistic stressor (i.e. breast cancer diagnosis) with clear onset, as opposed to an acute laboratory stressor (Carpenter et al., 2010) or a stressor of long duration, with a slower onset (i.e. caregiving) (Kiecolt-Glaser et al., 2010). Recently, a similar effect was observed in rodents. That study showed early life stress (maternal separation) to not only depress NKCA but to also increase tumor colonization in adult offspring subjected to chronic restraint stress (Nakamura et al., 2011).

The biological mechanism(s) linking childhood emotional neglect/abuse to reduced NKCA in women diagnosed with breast cancer is not clear. It is possible that women with such a history have higher cortisol levels, placing them at greater risk for cortisol-mediated reduction in NKCA (Webster Marketon and Glaser, 2008). Exposure to early life stress alters responsiveness of the HPA axis (Heim et al., 2000a,b; LaPrairie et al., 2010). More recently, early life stress was shown to result in epigenetic modification of stress response systems, especially the HPA axis, as reviewed (Mathews and Janusek, 2011). Evaluations of early life stress in rodents found that adult offspring of low nurturing mothers display anxiety-like behaviors and heightened HPA stress reactivity (Liu et al., 1997; Zhang and Meaney, 2010). This has been linked to reduced glucocorticoid feedback consequent to epigenetic modification of the proximal promoter of the glucocorticoid receptor within the hypothalamus (Francis et al., 1999; Weaver et al., 2004). A similar epigenetic modification to the glucocorticoid receptor gene promoter was observed in human suicide victims with a history of child abuse (McGowan et al., 2009). Further, we show epigenetic (histone) modifications to be associated with the functional activity of PBMC of women diagnosed with breast cancer. These epigenetic modifications were exhibited only during periods of increased psychosocial stress and were reversed when the stress dissipated (Mathews et al., 2011). Whether epigenetic modification, consequent to childhood adversity, underlies the profile of behavioral and immune dysregulation we observed in women with breast cancer requires further investigation.

It is important to understand the influence of childhood adversity on behavioral and immune outcomes in individuals with a serious disease, like cancer. Few studies have done so. A limitation inherent to such studies, including this one, is that it is not realistic to obtain baseline (pre-diagnosis) data. It is conceivable that women exposed to childhood adversity have greater behavioral symptoms and immune dysregulation prior to breast cancer diagnosis, contributing to our observations at initial assessment. Yet our findings are consistent with the literature demonstrating that childhood adversity exerts long-lasting effects resulting in increased stress responsivity during adulthood (Heim et al., 2008; McLaughlin et al., 2010b); thus, the possibility that women are responding more intensely to the stress associated with breast cancer remains plausible. Moreover, this possibility is strengthened in that we observe worse trajectories in perceived stress, quality of life, and circulating IL-6 (i.e. beyond initial assessment) for women who have experienced childhood physical neglect. These results suggest that childhood physical abuse results in slower recovery from the breast cancer experience. Findings from this study were derived from a relatively limited number of women and this can potentially compromise the reliability of the model estimates. However, estimated reliabilities for the initial status and growth rates ranged between 0.62 and 0.85, indicating that the variability in the presented models are likely due to systematic relations between growth estimates and child adversity factors. The longitudinal design and the application of growth curve modeling adds considerable strength to the design, as this approach provides valuable insight regarding intra-individual and inter-individual differences in behavioral and immune outcomes of women across the breast cancer trajectory.

With more women surviving breast cancer, it is increasingly important to understand those factors that can predict worse adjustment and predispose to protracted psychological and immunological recovery from this stressful experience. This is not only essential from the standpoint of quality of life, but also important in that restoration of NKCA after cancer treatment allows for optimal defense against nascent tumor cells that may remain after completion of surgery and adjuvant cancer treatment (Avraham and Ben-Eliyahu, 2007; Ben-Eliyahu, 2003; Lutgendorf et al., 2007).

Conflict of Interest

The authors of this manuscript have nothing to declare.

Acknowledgments

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